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The Current Status and Future Development of the HPV Vaccine

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Abstract. The introduction of the HPV vaccine in 2006 significantly decreased the prevalence of cervical cancer in the populace. Preventive HPV vaccinations have produced impressive outcomes based on the HPV mechanism. However, there is still great room for development in therapeutic vaccinations. In addition, there are still many issues and skepticisms surrounding the safety, efficacy, and sexuality of the HPV vaccine. In a nutshell, the human papillomavirus is a widespread human infection that poses a major risk to human health by increasing the risk of malignant tumors like cervical cancer. The WHO is developing a global strategy to eradicate cervical cancer, and the HPV vaccine is successful in reducing HPV infection and the illnesses it causes. Future commercial manufacture of the 14-valent HPV vaccination will greatly contribute to the implementation of this strategy.

Keywords: HPV, Vaccine

1. Introduction

In nature, there is an ancient virus that widely infects vertebrates, called papillomavirus (PV), with a history of millions of years. In the 1930s, American scientists isolated cottontail rabbit papillomavirus (CRPV) from snow rabbits for the first time, and subsequent studies found that the virus could cause tumors in rabbits. After CRPV was isolated and identified, many other PVs such as bovine papillomavirus (BPV) and canine oral papillomavirus (COPV) were also isolated and identified one after another [1]. In the 1970s, with the rapid development of molecular biology technology, people realized that there are great differences between PV and polyomavirus in terms of gene sequence, transcription mode, and homology of encoded proteins, so PV was classified as Papillomaviridae by the International Committee on Taxonomy of Viruses (ICTV) in 2000. In 1983 and 1984, the German Zur Hausen research group isolated human papillomavirus HPV16 and HPV18 strains from cervical cancer tissue, revealing the close relationship between HPV infection and cervical cancer [2]. In 2006, the first HPV vaccine of American Merck Company was launched, making cervical cancer and condyloma acuminatum caused by HPV preventable diseases.

Infections and precancers have decreased since the HPV vaccine was initially introduced in the United States in 2006 [3]. The HPV vaccine has its unique advantages as one of the methods of treating cancer, however, some specific issues also exist. The specific problems include side effects, safety concerns, fertility concerns, sexual concerns, as well as ethical considerations.

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This paper reviews the mechanism and the bottlenecks of HPV and the latest research progress on its preventive and therapeutic vaccines and provides ideas and references for innovative research on other virus vaccines.

2. HPV immunological mechanism

2.1. Title

The innate and adaptive immunity of the human immune system could control and clear the infected HPV, so most infections are self-limiting. Studies have shown that more than 90% of infected people would clear the virus within three years [4]. However, because HPV has multiple mechanisms to escape the immune system, a small number of people could still become persistently infected.

As shown in Figure 1, after physical damage to the skin or mucous membrane, the virus comes into contact with basal cells, at which point the first line of immune defense, also known as innate immunity, kicks in, with natural killer cells (NK) and macrophages. Under normal circumstances, the killing inhibitory receptor (KIR) on NK cells binds to the major histocompatibility complex (MHC) class I molecules to inhibit its killing effect on normal cells. However, HPV infection might downregulate the MHC class I molecules and initiate the activation. In addition, various cytokines such as interleukin-2 and interferon also play a role in clearing and inhibiting virus infection [5].

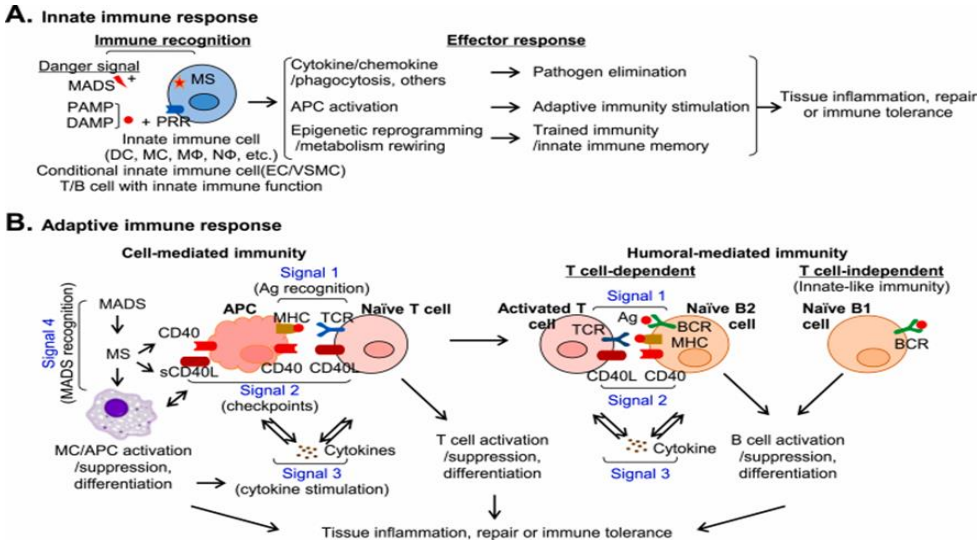

Figure 1. A description of the innate and adaptive immune systems.

At the infection site, dendritic cells are activated as a result of antigen uptake and processing by these cells. This prompts their movement into nearby lymphoid tissue and accelerates the development of effective antigen-presenting cells (APCs). Short peptides that have been digested into foreign antigen and presented by APCs are recognised by naive T cells. This causes the activation of T helper cells and the release of several tiny proteins and cytokines. Supporting the humoral response, T helper cells promote the development of B lymphocytes into memory B cells or plasma cells that secrete antibodies. Memory B cells retain information about the foreign antigen to produce antibodies more quickly when exposed to the same antigen again. Plasma cells manufacture antibodies including IgA and IgG. The cell-mediated response, which enables the activation of cytotoxic T lymphocytes and the production of memory T cells, is promoted by another fraction of T helper cells. They promote the innate immune system's activation of macrophages and natural killer cells. Natural killer cells and cytotoxic T cells can move to the contaminated area and eliminate pathogen-infected cells there.

As the second line of defense of HPV immunity, adaptive immunity needs to go through recognition, presentation, and effect. The immune response time is long but specific, has immune memory, and is

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still an important part of HPV immunity. CD8+ cell-mediated cytotoxic T lymphocyte (CTL) killing can clear infected cells, and E6 and E7 have multiple CTL epitopes that can cause specific cell killing [6]. After HPV infection, the body would produce antibodies against various proteins such as L1, L2, and E6. Among them, L1 antibodies account for the largest proportion, but most of them are type-specific antibodies, which are difficult to produce type cross-immune protection. The antibody molecules of HPV are mainly IgG and IgA, of which IgA is further divided into serotypes and secretory types. In the early stage, it was believed that its role in the mucosa was greater than that of IgG. IgG is mainly distributed in the serum and can penetrate the surrounding tissue through the blood vessel wall. However, later clinical trials proved that IgG antibodies play a major role in anti-HPV infection [7].

Although the HPV genome is simple, many complex mechanisms have evolved to evade the host's immune surveillance and clearance. In the early stage of HPV infection, the expression of early antigens of the virus is low, and the late antigens are not expressed. In the later stage, the late antigens are expressed in large quantities when they migrate to the surface layer farther from the basal cells and would not cause cell lysis, so it is difficult to cause an effective response of the immune system [8]. L2 is vital in the immune escape of HPV, mainly by preventing the increase in the number of immune-related signaling molecules on the surface of Langerhans cells and inhibiting their ability to activate T cells. In addition, some types of E6 and E7 can down-regulate the expression of type I IFN by interfering with the cell cycle [9].

3. The challenges of HPV vaccines

Currently, there are no specific ways to prevent this disease. All the temporary methods used to reduce the risk of getting the disease are concerned with reducing the risk of getting cardiovascular diseases and preserving cognitive ability. The main idea is to develop a healthy lifestyle.

3.1. Side effects

Like any drug, vaccines have some side effects. To prevent teens from fainting due to vaccination and injuries due to fainting, they are usually advised to sit or lie down for about 15 minutes after vaccination. Moreover, severe allergies to latex or yeast need to be considered in advance to prevent strong adverse effects after vaccination [10].

Although, the technology inevitably contains a few side effects, and these side effects also appear to varying degrees depending on the individual. Some adolescents may not experience the above reactions, while others may be more severe, but these are normal phenomena of vaccination. These side effects are very mild compared to the help the vaccine brings to the body. It's important to note that HPV vaccines are made from a non-contagious virus, which means they cannot cause HPV infection or cancer, concerns related to this issue can be omitted.

3.2. Safety concern

Many people may be concerned about the safety implications of the HPV vaccine, the truth is that every HPV vaccine available on the market such as the 9-valent HPV vaccine (Gardasil® 9), quadrivalent HPV vaccine (Gardasil®), and bivalent HPV vaccine (Cervarix®) has undergone rigorous safety testing before it is approved and marketed, and more than 15 years of monitoring have shown that the vaccine is sufficiently safe. As of July 23, 2021, 135 million doses of the HPV vaccine have continued to show that the vaccine is safe and effective since it was licensed. To date, none of the deaths that have occurred after vaccination has been directly related to the vaccine. The current safety assurance of the vaccine in society includes close monitoring by the Centers for Disease Control and Prevention (CDC) and the FDA, and all problems found will be reported to the health commissioner, health care professionals, and the public as soon as possible. In addition, the HPV vaccine can also provide people with protection that lasts for a long time. By tracking the people who received the HPV vaccine for 12 years, it was found that the protection of the vaccine HPV is still very effective. There is no evidence to prove that the protective ability of the vaccine will decrease over time [11].

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3.3. Fertility concerns

Some people may associate HPV with fertility problems, and in fact, it is people who are not vaccinated against HPV who face greater fertility limitations. The rationale is that people who are not vaccinated first have a significantly increased prevalence compared to the vaccinated population. After developing cancer caused by HPV, treatments such as hysterectomy, chemotherapy, or radiation therapy can greatly limit the fertility of women. Treatments for cervical precancers can also lead to cervical problems.

3.4. Sexual concerns

According to statistics, the reasons given by parents for not vaccinating include the safety concern mentioned above, lack of necessity, lack of knowledge about vaccines, the belief that children lack sexual activity, and gender issues [12]. Among them, concerns about sexual activity are raised in many statistics and reports. Parents don't want vaccinations to encourage their children to engage in sexual misconduct. The solution is to give children as much sex education as possible and encourage teenagers to use safety measures such as condoms.

3.5. Ethical considerations

In 2014, Navarro-Illiano and colleagues published a thought-provoking summary argument on the ethical considerations of universal HPV vaccination, while Spain was considering implementing an HPV vaccine program. Because sexual contact is the main route of HPV transmission, the main ethical are all related to it. The first problem is whether people who choose to abstain from sex should be vaccinated, which is raised because determinative abstinence (especially in early age groups) is a very uncertain parameter16. From a scientific standpoint, it appears that the antibody titer developed at a younger age is highest between the ages of 9 and 14. But often children at this age don't have a very good awareness of sexuality, which is why parents eventually reserve the right to decide whether to vaccinate their child. A potential solution to this problem is to focus on children's sex education to reduce high-risk sexual behaviors. The second problem is about the HPV vaccine manufacturer recommending the product to parents [13]. Recommending the HPV vaccine to parents and patients may be broader and more important than the first issue. Due to the commercial, clinical, and public association, the public will raise different levels of concerns including safety, economics, and so on. So as with most other interventions, parents can seek the advice of a clinician for vaccination.

4. Research progress of HPV vaccine

The vaccine is one of the greatest inventions in human history, and vaccination against HPV is the most economical and effective method to prevent HPV infection and related diseases. The immune response caused by HPV natural infection is weak, and it is difficult to produce sufficient titers of antibodies to neutralize the invading virus. Vaccination with HPV preventive vaccine can stimulate the body to produce high titers of neutralizing antibodies to clear the invading virus. Clinical results show that neutralizing antibodies produced by HPV vaccines can penetrate the blood vessel wall to reach the infection site and combine with the virus to make it lose the ability to infect cells. Both L1 and L2 are good prophylactic vaccine candidate proteins.

HPV vaccine vaccination for adolescent females combined with careHPV screening for adult females every five years is a cost-effective strategy for cervical cancer prevention and control. A follow-up study from 2006 to 2017 of the latest HPV vaccination population in Sweden showed that completing HPV vaccination before the age of 17 could reduce 88% of the infection. The incidence of cervical cancer can be reduced by 53% when vaccinated between 18 and 30 [14]. It can be seen that HPV vaccination can significantly reduce the risk of cervical cancer. The earlier the HPV vaccination and the younger the vaccination age, the better the effect of preventing cervical cancer. HPV has strict species, and tissue specificity infects highly undifferentiated epithelial cells and is difficult to culture on a large scale in vitro. Therefore, the currently marketed HPV preventive vaccines are all VLP forms of the L1 protein. Their structure is highly similar to natural HPV and has good immunogenicity. After vaccination, the

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immune body can produce high titers of neutralizing antibodies against the vaccine-type HPV. In addition, this vaccine is safe because it does not contain the genetic components of the virus, and there is no possibility of carcinogenesis.

There are four kinds of HPV vaccines on the market, all developed based on L1-VLP. In addition to the 4 HPV vaccines already on the market, many vaccines have also entered the clinical stage, including vaccines with L2 peptides as antigens and recombinant adenovirus (Ad) vector vaccines targeting oncoproteins, but most of them are still based on HPV L1 protein as an immunogen. Most of the HPV vaccines that have entered the clinical stage abroad are therapeutic vaccines.

The currently marketed prophylactic vaccines are prepared with HPV L1-VLP containing the wild-type protein sequence as the antigen and mixed with multiple types. Among them, the 9-valent vaccine Gardasil 9 (about 90%) has the widest protection range. Its protective mechanism induces the body to produce high titers of neutralizing antibodies [15]. However, HPV is highly type-specific, and it is difficult for antibodies induced by a single type of VLP to cross-neutralize other types, making it difficult for existing HPV vaccines to protect other HPV types other than those covered by the vaccine. Currently, there are more than 15 known high-risk HPV types, and the distribution of cervical cancer-related HPV types in different regions is also quite different. Among them, the distribution of HPV 59 and 35 beyond the protection range of the 9-valent vaccine accounts for 9.8% and 4.4% of the total in West Africa. A new generation of vaccines must be considered to achieve a wider range of type protection. However, continuing to increase the new type of HPV L1-VLP would increase the complexity of the production process and potential side effects, and the mixed immunity of multiple different types of VLP in the body may interfere with the immune response of different types of immunogens in the body, affecting the protective effect. Therefore, the research of HPV preventive vaccines must break through the limitation that the original vaccines only produce type-specific protection and take a different approach in theory and technology.

Studies on the structure of type-specific neutralizing epitopes of HPV 58 and 59 give hints on the new direction of the HPV vaccine. Firstly, the strict type-specific structural basis of HPV is that type-specific neutralizing epitope amino acids are highly conserved in the same type of protein sequence, but there are great differences between different types. These amino acids are related to HPV infection of host cells [16]. Secondly, most of the type-specific neutralizing epitope amino acids are located in the loop region on the surface of HPV L1 pentamer, and the structural loop regions where the key amino acids of different types of neutralizing epitopes are located are not the same. Then, a type-specific neutralizing epitope key amino acid was replaced on the HPV L1 protein with a close type evolutionary relationship. The mutated VLP had the activity of binding the specific neutralizing antibody of the transplanted type, indicating that type-specific neutralizing epitopes can be remodeled by transplantation. Transplantation of neutralizing epitopes between types can potentially construct different types of protective antigens.

Based on the above results, an ideal design of a new generation of vaccines can be carried out. The evolutionary relationship between the major structural protein L1 of 20 major HPV types classified by the International Agency for Research on Cancer (IARC) can be analyzed first and compared with the capsid pentamer crystal structure conservation of 8 types of HPV. The type-specific dominant neutralizing epitope is composed of the type-specific amino acids on the surface and the conserved overall structure of the virus particle. A homologous replacement method for structural information can achieve antigenicity and immunogenicity of various types of HPV in a molecularly engineered HPV58/33/523 type chimeric VLP. Also, the research groups can further use crystal structure and cryo-electron microscopy (cryo-EM) structure determination to reveal the structural basis for cross-protection of chimeric VLPs. In addition, they can design and verify the versatility of the molecular design strategy, which can open up a new way to develop a new generation of HPV vaccines that can protect 20 types of HPV infection by seven chimeric VLPs. Compared with the currently marketed preventive vaccines, the new HPV vaccine based on this design can reduce the types of vaccine particles, thereby reducing the immunization dose, the difficulty of the production process, and the production cost, and at the same time improving the scope of vaccine protection.

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5. The prospect of the HPV vaccine

In the past 20 years, the research on HPV preventive vaccines has made great progress. In addition to the four vaccines that have been marketed, many vaccines have completed Phase I and II clinical trials and are undergoing more in-depth research. However, there is still a gap between the research and clinical application of HPV therapeutic vaccines, especially the existence of possible side effects and low immunogenicity in clinical practice, the strict species specificity of HPV virus, the difficulty in establishing animal models to evaluate the immune effect of vaccines, and the security of the vaccine. In addition, the research of preventive and therapeutic vaccines should be considered a lot, such as how to choose the best vaccine strategy, such as vector optimization, selection of efficient and simple expression system, construction of integrated chromosomal expression strains, rational optimization of dose bottlenecks, and use of interdisciplinary methods such as structural biology to develop rational and efficient new types of vaccines design, optimization of vaccine delivery methods, development of high-efficiency new adjuvants, changes in the prevalence of various types in the population, exploration of strategies such as combination therapy, and rational selection of vaccine conditions for clinical application, etc.

Therapeutic HPV vaccines are mainly aimed at intervening in the carcinogenicity of HPV, and preliminary progress has been made. However, they have not yet achieved results in treating condyloma acuminatum, atypical hyperplasia, and cervical cancer. Therefore, it is still necessary to strengthen the research on HPV virology and the pathogenic mechanism of infection. The 14-valent HPV vaccine may be able to quickly cover all 12 high-risk oncogenic HPV types announced and the two most important HPV types that cause condyloma acuminatum if the technical threshold of HPV vaccine production can be crossed.

HPV vaccine development uses genetic engineering technology to produce HPV virus-like particles (HPV-VLP) without viral genes. Because HPV-VLP does not contain viral genes, HPV-VLP has no replication function, so it would not cause the risk of HPV virus infection in the human body. However, the HPV-VLP coat is similar to the HPV viral coat and has the same immunogenicity. Therefore, using HPV-VLP as the vaccine antigen, an immune response can be generated after immunizing animals or humans, similar to that produced by HPV virus infection. Therefore, vaccine recipients can gain immunity, reducing the risk of persistent HPV infection and consequent cancer risk.

The HPV vaccines currently on the market and under development are based on the virus-like particle (VLP) technology formed by the L1 protein of recombinant HPV. Only VLPs with the same structure as the natural virus can induce immunogenicity to prevent diseases caused by HPV infection. The formation of the correct structure of VLP is not only based on the correct gene sequence but also the culture conditions and intracellular microenvironment. Therefore, the expression and maintenance of VLP and the purification process to optimize the correctness of its structure are the technical thresholds and main challenges for the production of HPV vaccines.

Therefore, the 14-valent HPV vaccine can rely on industrial technologies such as insect cell baculovirus production technology, purification technology, and virus-like particle disassembly technology to systematically optimize the whole process parameters of the virus-like particle production process. In this way, many technical difficulties and technical bottlenecks such as difficulty expressing HPV-type virus-like particles, low expression levels, imperfect particle assembly, and poor stability can be broken through. Thus, a high-efficiency and highly similar production process technology can be established for all 14 important virus-type virus-like particles. Process reliability, high throughput, and similarity of process steps between subtypes would greatly increase the competitiveness of 14-valent HPV vaccines.

In addition, through preclinical research, researchers can establish several key production processes for eukaryotic cells to produce high-quality HPV-VLP. Through the application of this technology, the feasibility and competitiveness of 14-valent HPV vaccine development can be improved. It would be beneficial to increase the utilization rate of the HPV vaccine among the appropriate age groups.

When the 14-valent HPV vaccine is introduced, it is expected to offer the highest coverage of HPV vaccines to school-age women in the world. After large-scale vaccination of the 14-valent HPV vaccine,

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it is expected that the number of new cases of cervical cancer could be reduced to no more than 4,000 in the future, with significant social and economic benefits.

The HPV vaccine has become one of the most popular medicines in the second-class vaccine market in the world. As more companies participate in the vaccine industry, not only the market would receive more vaccine supplies, but there would soon be more female populations of the right age favoring more-valent HPV vaccines with higher protection rates as citizens' awareness of HPV vaccines and socioeconomic conditions improve. People of appropriate age can obtain a higher HPV preventive protection rate by vaccinating a single drug, which would help to expand the choice of HPV vaccine and medication for the appropriate age group, increase their willingness to be vaccinated, increase the use rate of the HPV vaccine among them, and reduce the risk of developing cancers such as cervical cancer.

Also, early studies found that the C-terminus of HPVL1 has a turn-back structure extending into the adjacent pentamer. A conserved cysteine in this structure forms a disulfide bond with the conserved cysteine of the EF loop in the adjacent pentamer [17], and these two mutations would cause the pentamer to fail to form VLP. In HPV16, these two sites are C175 and C428, and the corresponding positions of other types of cysteine are also named through sequence alignment for C175 and C428. To further improve the coverage of multi-type vaccines, the aggregation of multiple epitopes required in designing other hypervariable virus vaccines and vaccines targeting tumor neoantigens can also be considered.

6. Conclusion

In summary, although the public is somewhat skeptical about HPV vaccines, it is undeniable that they have played an important role in the Global Strategy for Cervical Cancer Elimination shortly. The new generation of HPV vaccine design has introduced structure-based vaccine rational design, and some progress has been made. These cases would also provide a reference for developing other complex and variable virus vaccines. HPV therapeutic vaccines are mainly aimed at intervening in the carcinogenicity of HPV, and preliminary progress has been made. However, no results have been achieved in treating condyloma acuminatum, dysplasia, and cervical cancer. Therefore, it is still necessary to strengthen the research on HPV virology and the pathogenic mechanism of infection. With the further in-depth study of HPV, it is expected that preventive and therapeutic vaccines can be combined shortly to provide the ultimate weapon for protecting human beings from HPV infection and the malignant diseases caused by it. In a word, Human papillomavirus widely infects human beings, can lead to the occurrence of malignant tumors such as cervical cancer, and seriously endanger human health. In the future, the mass production of the 14-valent HPV vaccine would significantly contribute to this strategy's implementation.

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